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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,917	04/11/2006	Yipu Feng	13695/1	5543

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EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

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07/21/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,917	FENG ET AL.	
	Examiner	Art Unit	
	Brian-Yong S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-8* is/are pending in the application.

4a) Of the above claim(s) _ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Status of Application

1. Acknowledgement is made of applicant's remarks filed on 05/17/2010.

2. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over. Chang et al. (Acta Pharmacologica Sinica, August 2003, 24(8), pp. 796-804), and further in view of Lee et al. (US 6716822) and Izozumi et al. (Tokai J Exp Clin Med., vol. 23, No. 3, pp. 103-117, 1998).

Chang teaches use of 3-n-butylphthalide, preferably l-3-butylphthalide (NBP) as effective agent for improving ischemia-induced apoptosis, particularly transient focal cerebral ischemia-apoptosis (abstract; materials and methods; discussion, especially para. 3 of page 803), wherein said compound is administered in dosage amounts in range from 5mg-20mg/kg to a subject after the ischemia (Figures). Chang discloses that "neuronal cell loss after cerebral ischemia involved apoptosis…the apoptotoic process largely contributed to the expansion of the ischemic damage"; "antiapoptotic maneuvers could reduce neuronal death and infarct volumne"; and that the beneficial effects NBP on cerebral ischemia-induced apoptosis, by inhibiting apoptosis, might be useful for the treatment of ischemic cerebrovascular diseases (page 797, column 1, para. 1; page 803, column 1, last paragraph).

Lee is being provided as a supplemental reference to demonstrate the state of the art knowledge in using apoptosis-inhibiting agent for the treatment of cerebral infarction (abstract).

Izozumi is being provided as a supplemental reference to demonstrate the state of the art knowledge in using focal cerebral ischemia model as an experimental model of cerebral infarction (page 106, column 1, para. 3 through page 108, column 1, para. 1).

The teaching of Chang differs from the claimed invention in the use of said NBP in the therapeutic treatment of cerebral infarction. To incorporate such teaching into the teaching

Chang, would have been obvious in view of Lee who teaches or suggest the utility of antiapoptotic agent for the treatment of (cerebral infarct) stroke and Izozumi who teaches the focal cerebral ischemia animal model as a well recognized experimental model of cerebral infarction.

One having ordinary skill in the art would have expected that there is nexus between neuronal apoptosis and ceberal infarction or stroke. Thus, one having ordinary skill in the art would have been motivated to modify the Chang, with the reasonable expectation of success, to arrive at the instant invention.

As evidenced by Izozumi, one having ordinary skill in the art has basis for perceiving those studies provided in Chang as constituting recognized procedure with clear relevance to therapeutic utility in treating cerebral infarction, in animals or humans.

The prior art does not disclose the underlying pharmacological mechanism of "to reduce the volume of the cerebral infarction". However, the fact that the applicant may have discovered a new pharmacological mechanism for L-butylphthalide of formula (I) is not considered patentably distinctive over the prior art which are directed to the same therapeutic application (for the treatment of cerebral infarct induced by focal cerebral ischemia). The examiner considers that such property deems to be a necessary consequence of what is deliberately intended in the prior art method. . Thus, the references in combination make obvious the instant invention.

Applicant has presented no evidence to establish the unexpected or unobvious nature of the claimed invention, and as such, claims 608 are properly rejected under 35 U.S.C. 103.

Response to Arguments

4. Applicant's arguments filed 05/17/2010 have been fully considered but they are not persuasive.

Applicant's argument in the response takes the similar position as the previous argument filed 06/16/2009 that there is no clear relationship between the inhibition of apoptosis caused by l-butylphthalide and the treatment of cerebral infarct. Furthermore, applicant alleges that there is no clear relationship between the inhibition of apoptosis caused by l-butylphthalide and the reduction of the volume of cerebral infarct. Applicant argues that the relationship of neuronal apoptosis and infarct size is complicated such that a person of ordinary skill in the art would not have reasonable expectation at the time of the invention was made that l-butylphthalide would reduce the volume of the cerebral infarct.

Again, this argument is not found persuasive. Contrary the applicant's argument, the nexus between the neuronal apoptosis and the cerebral infarction or stroke was well known at the time of the invention was made as discussed above in US'822 (see also USP 6399576, USP 6106830, and USP 2002/0025985). For instance, US'576 discloses a method of inhibiting apoptosis, thereby treating apoptosis-related diseases including ischemic disease such as cardiac infarction and cerebrovascular disease such as cerebral stroke, cerebral infarction by administering an apoptosis inhibitor such as batroxobin (column 2, lines 43-57); US'985 discloses a method of treating a disease or condition associated with apoptosis such cerebral infarction by administering an apoptosis inhibitor such as 15-keto-prostaglandin. Thus, one having ordinary skill in the art, in light of ponderous evidences showing nexus between the neuronal apoptosis and the cerebral infarction or stroke at the time of the invention was made,

would have been motivated to modify the Chang, with the reasonable expectation of success, to arrive at the instant invention.

Alternative, regardless of the underlying mechanism of actions, 3-n-butyphthalide (NBP) is known have "many anti-ischemic effects, including reducing the area of cerebral infarction in MCAO, attenuating neuronal damage after delayed cerebral injury, ameliorating mitochondria dysfunction during cerebral ischemia…ameliorating brain edema regional blood flow in MCAO…" (page 796, column 2, para. 2 of Chang et al.; see also page 1, line 20 through page 2, line 18 of the specification) and l-NBP is more active form than d-form. Thus, one having ordinary skill in the art would have been motivated to use the l-NBP because a single enantiomer would have been expected to be similarly useful as the racemic mixture. Since the feature of reducing the volumne of the cerebra infarct is expected (inherent) feature of the l-NBP when it is administered to a patient having cerebral infarct or focal cerebral ischemia, the cited references in combination make obvious the instant invention.

Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. No Claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

/Brian-Yong S Kwon/
Primary Examiner, Art Unit 1614